Case Report
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A Case of Primary Adrenal Lymphoma: How Do We Detect Early Progression to Adrenal Insufficiency?

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Abstract

Introduction:

Diffused large B cell lymphoma (DLBCL) is a type of aggressive non-Hodgkin's lymphoma. Non-Hodgkins lymphoma arising in endocrine organs account for 3% of extra-nodal malignant lymphoma, and Primary adrenal lymphoma account for only 0.2% of them. Primary adrenal lymphoma involves the bilateral adrenals in 70% cases, and can cause adrenal insufficiency even if the lesion is unilateral.

Case Description:

We present a 60-year-old female, who presented with constitutional symptoms and dyspnoea. On examination she was underweight, had marginally low blood pressure, and was desaturated. She had hyponatremia and high lactate dehydrogenase levels. 2D echocardiogram showed two echogenic masses: one in the anterior pericardial space, and another in the right atrium obstructing the tricuspid origin. Ultrasound scan showed a left suprarenal mass, and bilateral pleural effusions. CECT showed the same enhancing mass involving tricuspid valve, which was extending into the right atrium, and right ventricle causing luminal narrowing and an enhancing solid lesion in the left adrenal gland (HU 30.8). 9am cortisol was 422 nmol/L, with high serum ACTH. She developed hypotension which responded to IV hydrocortisone. Adrenal biopsy revealed high grade DLBCL with Ki 67 index of 80%. She suddenly succumbed before definitive treatment.

Conclusion:

Adrenal insufficiency in the setting of a unilateral non secretory adrenal lesion should rise the suspicion of Primary adrenal lymphoma rather than adrenal metastasis. Similarly, when biopsy of an adrenal lesion reveals Primary adrenal lymphoma rather than metastasis, there should be a higher index of suspicion to detect the presence of or progression to early adrenal insufficiency, even if the lesion is unilateral.

Keywords: Primary adrenal lymphoma, Diffused large B cell lymphoma, Adrenal insufficiency, Cortisol

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Introduction

Diffused large B cell lymphoma (DLBCL) is an aggressive form of non-Hodgkin's lymphoma (NHL), accounting for 30% of lymphomas [1]. NHL arising in endocrine organs accounts for 3% of extra-nodal malignant lymphoma, and PAL accounts for only 0.2% of them [1,2]. PAL is diagnosed by histologically confirmed lymphoma involving one or both adrenal glands, with no previous history of lymphoma, or the adrenal lesion being significantly dominant if lymph nodes or tissues other than the adrenals are involved 3. DLBCL accounts for 86% of PAL, and involves the bilateral adrenals in 70% of cases[1]. Adrenal insufficiency (AI) is seen in 61% of cases of PAL [2].

Case Presentation

A 60-year-old female, with known hypertension, presented unwell with one month history of shortness of breath on exertion, hyperpigmentation, loss of weight, loss of appetite, fatigue and occasional loose stools. She had no family history of malignancy. On examination, she had a BMI of 17 kg/m^2, blood pressure was 100/70mmHg, and a heart rate of 100 beats per minute. She had reduced intensity of breath sounds bilaterally, and oxygen saturation was 94% on air.

She had hyponatremia of 131 mmol/l, serum osmolality of 278 mOsmol/kg, urine osmolality of 197 mOsmol/kg, and urine sodium of 30mmol/l. She had high lactate dehydrogenase levels. (table 1) 2D echocardiogram showed an echogenic mass in the anterior pericardial space, and another echogenic mass in the right atrium measuring 33mm x 30mm, obstructing the tricuspid origin. The right atrium was dilated, with impaired right ventricular function. There was a pericardial effusion measuring 8mm anteriorly. The coronary angiogram was normal.

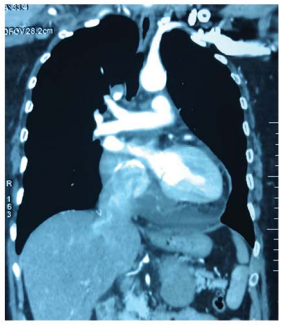


Figure 1: Contrast enhanced CT showed a large lobulated heterogeneously enhancing mass mainly involving tricuspid valve, which was extending into the right atrium, and right ventricle causing luminal narrowing. It extended into the pericardial space with a large pericardial effusion with a maximum thickness of 3cm, with no pericardial thickening. The lesion also extended into the adjacent supradiaphragmatic inferior vena cava. The right coronary artery was completely encased by the mass from its origin. Both lungs appeared normal with no mass lesions, but had few lymph nodes in the pre-tracheal and sub-carinal region measuring 8mm.

Ultrasound scan of the abdomen showed a left suprarenal mass, and bilateral pleural effusions. Contrast-enhanced computed tomography (CECT) of the chest and abdomen showed a lobulated heterogeneously enhancing mass mainly involving the tricuspid valve, which was extending into the right atrium, and right ventricle, causing luminal narrowing. It extended into the pericardial space with a large pericardial effusion with a maximum thickness of 3cm, with no pericardial thickening. The lesion also extended into the adjacent supradiaphragmatic inferior vena cava. The right coronary artery was completely encased by the mass from its origin. Both lungs appeared normal with no mass lesions but had a few lymph nodes in the pre-tracheal and sub-carinal region measuring 8mm. (Figure 1) In addition, there was a large contrast enhancing well defined hypodense solid lesion in the left adrenal gland measuring 7cm x 7.9cm x 7cm, with a Hounsfield value of 30.8 in the non-contrast phase. There were low-density areas in the lower pole of the spleen. (Figure 2)

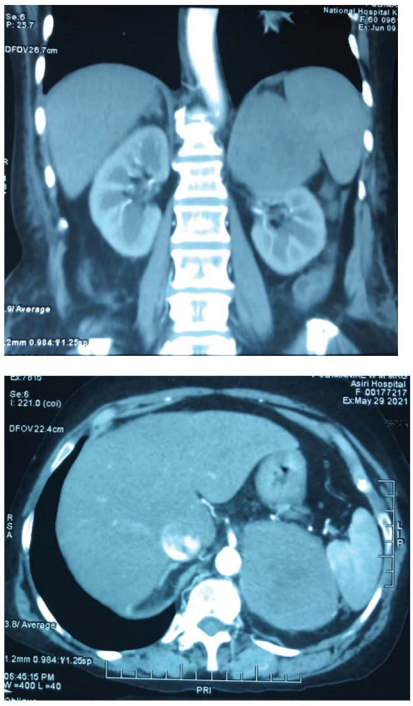


Figure 2: Contrast enhanced CT showed There was a large mildly enhancing well defined hypodense solid lesion in the left adrenal gland measuring 7cm x 7.9cm x 7cm, with a Hounsfield value of 30.8 in the non-contrast phase. There were low density areas in the lower pole of the spleen. No other enlarged lymph nodes were noted in the chest and abdomen.

Table 1: Basic investigations

Investigation	Finding
White blood cell count	4.65 x 109 (4 -11 x 109)
Haemoglobin	11.2 g/dL (12 -15 g/dl)
Platelet count	265 x 109 (150 -450 x 109)
Blood picture	Anaemia of chronic disease with no atypical cells
Lactate dehydrogenase	961 U/L (140 – 280 U/L)
antibodies to Human immunodeficiency virus 1 and 2	negative
Erythrocyte sedimentation rate	19 mm/1st hour (0 – 30 mm/1st hour)
C-reactive protein	21.6 mg/dL (0.3 -1.0 mg/dL)
serum creatinine	73 µmol/L (65.4 – 119.3 µmol/L)
Serum potassium	4.8 mmol/l (3.5 – 5 mmol/l0
Serum sodium	131 mmol/l (135 -145 mmol/l)
PH	7.4 (7.35 -. 7.45)
HCO3-	24 mEq/l (22 – 26 mEq/l)
Liver function tests and liver enzymes	normal

Table 2: Hormone profile

Hormone profile	Hormone level
ACTH	78.2 pg/mL (6- 48 pg/mL). 30.9 pg/mL (repeated one week later)
Thyrotroph stimulating hormone	2.53 mIU/L (0.4 -4 mIU/L)
9am testosterone	0.463 nmol/l (0.198 – 2.67 nmol/l for females)
24 hour urinary total metanephrine excretion	0.41 mg/24 hours (<1mg/ 24 hours).
Plasma aldosterone	23.07 ng/dL (7- 30 ng/dL)
plasma renin	36.14 mU/L (4.2 – 45.6 mU/L)
plasma aldosterone: renin ratio	0.638 ng/dL/mU/L (<3.7 ng/dL/mU/L)

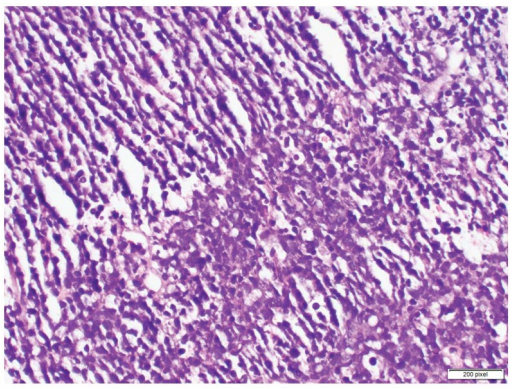
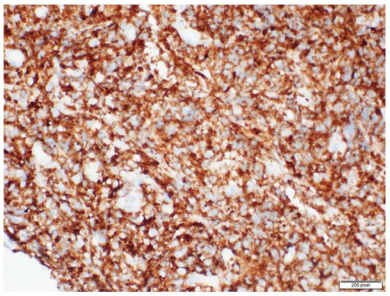
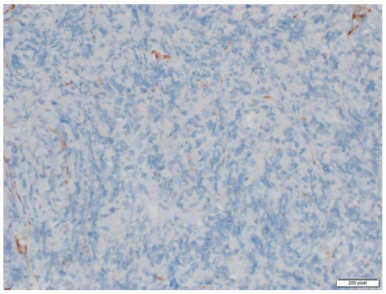


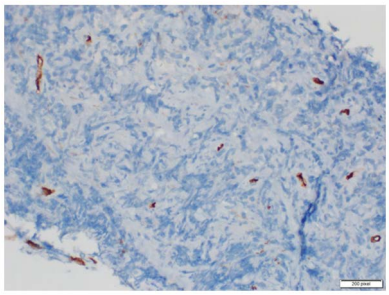
Figure 3: On high power field sections through the biopsy core show a neoplasm composed of sheets of atypical small round cells. The cells show hyperchromatic nuclei with irregular contours and scanty cytoplasm. Mitotic figures are brisk with atypical forms.



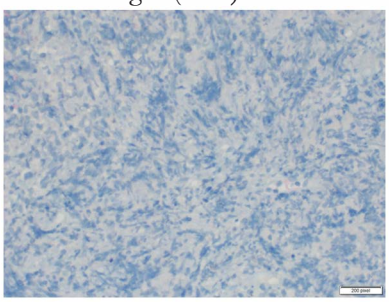
(a) Positive Leucocyte common antigen (LCA) stain



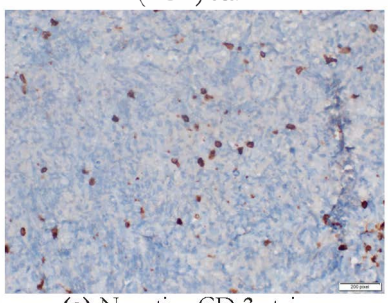
(b) Negative Pan-cytokeratin (PCK) stain



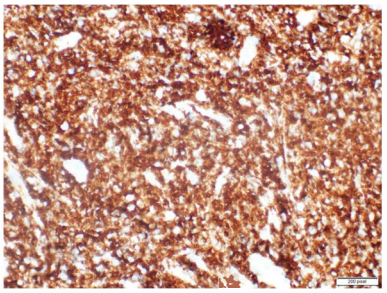
(c) Negative CD 34 stain



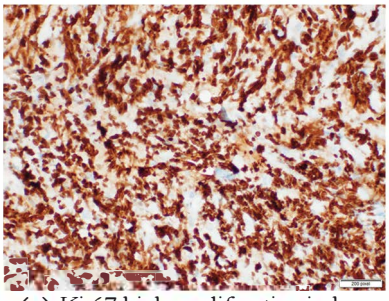
(d) Negative Smooth muscle actin (SMA) stain



(e) Negative CD 3 stain



(f) Strongly diffusely positive CD 20 stain



(g) Ki 67 high proliferative index

Figure 4: : Immunohistochemical staining of the tumour cells were strongly positive for LCA and negative for PCK, indicating the cells were of lymphocytic origin and not epithelial (a)(b). CD 34 stain negativity excluded a vascular neoplasm (c), and SMA stain negativity excluded a sarcoma (d). CD 3 negativity and CD 20 strong diffuse positivity confirms that the neoplastic cells are of B cell origin (e) (f). Ki 67 proliferative index was 80% indicating high proliferative activity (g)

9 am cortisol was 422 nmol/L, and serum adrenocorticotrophic hormone (ACTH) level was high at 78.2 pg/mL (6- 48 pg/mL). The ACTH level was repeated a week later, and it remained high. The rest of the hormones related to adrenal function were normal. Magnetic resonance imaging (MRI) of the pituitary showed no pituitary tumour. Short Synacthen Test (SST) was planned.

She developed low blood pressure of 70/50 mmHg. All antihypertensives were omitted, and her blood pressure improved with fluid resuscitation and a dose of intravenous hydrocortisone. She underwent ultrasound-guided biopsy of the adrenal mass. While awaiting the histology, she developed sudden cardiac arrest and sadly succumbed. Histology of the adrenal biopsy revealed an appearance consistent with a high-grade DLBCL. (Figure 3) On immunohistochemistry, the tumour cells expressed LCA and CD20 diffusely, occasional scattered cells expressed CD3 and staining for ACTH was negative. Ki 67 proliferation index was 80%. (Figure 4)

Discussion

The Endocrine Society guidelines suggest a cortisol of <140nmol/L and ACTH more than 2 fold the upper limit of the reference range being consistent with primary adrenal insufficiency (PAI). However, cortisol of <500 nmol/L in response to SST is required to establish the diagnosis of AI [4]. This patient, who had a 9 am cortisol of 422 nmol/L was planned to undergo SST to confirm AI, but died before it was performed. Evidence discussed in the Endocrine Society guideline states that an elevated ACTH in the presence of a normal cortisol can be the first sign of early primary adrenal insufficiency (PAI), which would explain the picture of cortisol and ACTH in this case [4]. The cut-off point for the ACTH level is debatable, as this is also influenced by analytical bias demonstrated in assays used for ACTH [4]. The ACTH of 78.2 pg/ml in this case, though not 2-fold the upper limit, is still clearly above the upper limit of 48 pg/ml for the tested assay. The guidelines state that in some cases of PAI, the ACTH level would be only above the quoted reference range, but may not always be 2-fold the upper limit [4]. A plasma ACTH exceeding 66 pmol/L (300 pg/ml) is the maximum stimulation required to produce cortisol from the adrenal glands [4]. Therefore, the early PAI in this patient likely stimulated increased ACTH secretion and only required a rise of 78.2 pg/ml to barely maintain the cortisol level at 422 nmol/L.

Mineralocorticoid deficiency may predominate in the early phase of evolving PAI [4]. Therefore, an elevated plasma renin concentration or activity, with an inappropriately normal aldosterone is suggestive of early PAI [4]. This patient's plasma renin was in the upper normal range, though we could not assess the renin activity.

She had hyponatraemia with high urine osmolality and urine sodium likely due to either syndrome of inappropriate antidiuretic hormone (SIADH) secondary to lymphoma or early AI or a combination of both. She had severe hypotension, likely due to cardiac outflow obstruction from the metastatic cardiac mass. This may have also been contributed by early AI. Her episode of severe hypotension responded to fluid resuscitation and IV Hydrocortisone, indicating AI had a predominant impact on her low blood pressure.

Non-secretory adrenal masses, which are contrast-enhancing with a Hounsfield unit of more than 10 could either be adrenal metastasis or primary adrenal lymphoma. Malignancy may cause "stress" on the adrenal glands, which can blunt the cortisol response[5]. Furthermore, severe weight loss associated with malignancy can reduce plasma corticosteroid binding globulin. If this is not met with a concurrent increase in cortisol secretion, the measured total plasma cortisol can be lowered [5]. Direct adrenal tissue infiltration and destruction by metastasis can impair cortisol production. However, unilateral adrenal metastasis does not generally cause AI, and is reported in only 6.1% of bilateral adrenal metastasis [6]. Adrenal glands have the ability to maintain their function until >90% of the adrenal cortex is destroyed. Therefore, even bulky bilateral adrenal metastasis can maintain the cortisol axis in the absence of AI [6].

In contrast to adrenal metastasis, PAL is more likely to cause AI and is seen in 61% of cases of PAL [7]. Although 70% of PAL cases are bilateral, even unilateral PAL can cause AI [1,7]. Bilateral PAL is at higher risk of causing AI compared to unilateral PAL, but 20% of cases of PAL associated with AI are unilateral, accounting to a significant proportion [7,8]. PAL tumour size showed little correlation with the occurrence of AI, and even very small PAL has been associated with AI [7,8]. In addition to direct tissue infiltration and destruction seen in adrenal metastasis, PAL has been suggested to have an additional mechanism of cytokine-related paracrine effect on the adrenal biochemical microenvironment as a possible explanation for the high likelihood of developing AI [7]. Therefore, when evaluating non-secretory adrenal masses, if AI is present in the setting of a unilateral adrenal lesion, the possibility of PAL is more likely than adrenal metastasis. Similarly, when a biopsy of an adrenal lesion has proven to be PAL rather than metastasis, there should be a higher index of suspicion to detect the presence or progression to early AI, even if the lesion is unilateral.

This patient had a cardiac mass causing cardiac outflow obstruction. Cardiac involvement is seen in 16% of lymphoma, and 13.6% of metastatic cardiac deposits are due to lymphoma [9]. DLBCL, which is an aggressive form of lymphoma, had a Ki67 proliferative index of 80% in this patient, indicating a high likelihood of progression to cardiac involvement. High-grade DLBCL has a low cure rate of 27%, with a median survival time of 6.6 months in uncured patients following treatment [10]. The survival in untreated patients could be a few weeks. 76% of deaths in DLBCL are due to the malignancy itself [10]. This patient's early sudden death was likely due to the progression of malignancy, and cardiac outflow obstruction by the tumour, and may have been contributed by possible early AI.

Conclusion

AI in the setting of a unilateral adrenal lesion should raise the suspicion of PAL rather than adrenal metastasis. Similarly, when a biopsy of an adrenal lesion has revealed PAL rather than metastasis, there should be a higher index of suspicion to detect the presence of or progression to early AI, even if the lesion is unilateral. High ACTH with normal serum cortisol, hypotension and hyponatremia could be indicators of early adrenal insufficiency.

Abbreviations:

DLBCL diffused large B cell lymphoma
NHL non-hodgkins lymphoma
PAL Primary adrenal lymphoma
AI adrenal insufficiency
PAI primary adrenal insufficiency
ACTH adrenocorticotrophic hormone
CECT contrast enhanced computed tomography
MRI magnetic resonance imaging.

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Author contributions & acknowledgements: KPJ and CNA were involved in treating the patient. KPJ wrote the case report, and this was supervised by CNA and NS. All authors have read and agreed to the final manuscript. We acknowledge all medical teams involved in managing this patient.

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